REMARKS

Claims 67-82 presently appear in this case. No claims have been allowed. The official action of April 20, 2005, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to an isolated polypeptide comprising the amino acid sequence of fragment C48 of the placental ferritin protein OFF1. The invention also relates to pharmaceutical compositions, isolated DNA molecules, expression vectors, host cells and methods of preparation of the polypeptide, as well as its method of use in treating rheumatoid arthritis.

The examiner has required restriction between Group I, including claims 67-82, and Group II, including claim 83, drawn to a second method of using the first-claimed product.

Applicant hereby affirms the provisional election made by telephone. Non-elected claim 83 has now been deleted. Thus, all the claims now present in the case are directed to the elected invention.

The examiner states that the application fails to comply with the sequence listing requirements. The examiner states that nucleotides at pages 15, 19, 27, Figures 1-5 and 7 are not in the sequence listing. This rejection is respectfully traversed.

The examiner's attention is respectfully invited to applicant's amendment of August 21, 2001, entitled "Response to Notification to Comply with Sequence Listing Requirements." This amendment amends pages 15, 19, 27 and the description of Figures 1-5 and 7, so as to specifically refer to SEQ ID NOs., all of which are in the Sequence Listing. Accordingly, this objection must be withdrawn.

It is noted, however, that a discrepancy appears in Figure 5 in that for amino acid 65, the amino acid is listed as Gln, while the nucleotide triplet is GAA, which codes for Glu. This typographical error is regretted. Attached hereto is a proposed amendment to Figure 5 in order to correct this typographical error and correctly show the amino acid as Glu. A new paper copy and computer-readable copy sequence listing is attached hereto, also correcting this error.

The following statement is provided to meet the requirements of 37 C.F.R. §1.825(a) and 1.825(b).

I hereby state, in accordance with 37 C.F.R. §1.825(a), that the amendments included in the substitute sheets of the sequence listing are believed to be supported in the application as filed and that the substitute sheets of the sequence listing are not believed to include new matter.

I hereby further state, in accordance with 37 C.F.R. §1.825(b), that the attached copy of the computer readable form is

the same as the attached substitute paper copy of the sequence listing.

The examiner states that the listing of references in the Search Report has not been considered as these do not comply with the requirements for an Information Disclosure Statement.

The examiner's attention is invited to the fact that all of the references in the Search Report were listed in a proper Information Disclosure Statement filed on October 30, 2001.

The examiner states that the IDS filed on October 30, 2001, fails to comply with 37 C.F.R. §1.98(a)(1), apparently only because each page of the list of references does not have the application number of the application in which the IDS is being submitted. This statement of the examiner is respectfully traversed.

The IDS submitted on October 30, 2001, used the form SB/08A and 08B from the PTO web site. Accordingly, these presumptively comply with the rules. Furthermore, applicant has reviewed 37 C.F.R. §1.98(a)(1) and can find nothing therein that requires that a listing of references attached to an IDS must have the application number of the application in which the IDS is being submitted on each page of the list. It is urged that there is no reason why the examiner should not consider the references submitted with the IDS of October 30, 2001.

Nevertheless, a copy of the attachment to that IDS is also attached hereto on which has been added on each page the serial number of the application. Consideration of the IDS of October 30, 2001, and all of the references cited therein and submitted therewith are therefore respectfully urged.

The examiner has objected to the amendment filed January 31, 2005, as introducing new matter into the disclosure. The examiner states that SEQ ID NO:5, filed in that amendment and SEQ ID NO:5 disclosed in PCT/IL99/00485 are not identical. This objection is respectfully traversed.

The examiner's attention is again invited to applicant's response of August 21, 2001, which clearly explains this alleged discrepancy. The last paragraph on page 7 clearly states that SEQ ID NO:3 has been deleted from the previously-filed sequence listing as SEQ ID NO:3 was a partial sequence of SEQ ID NO:1. The subsequent sequences have been renumbered accordingly in the substitute sequence listing. Accordingly, presently-identified SEQ ID NO:5 is identical to previously-appearing SEQ ID NO:6 in the PCT international publication. There is nothing in 35 U.S.C. §132(a) that prohibits an applicant from amending the specification as appearing in the PCT application as long as no new matter has been added. Clearly the elimination of SEQ ID NO:3 as being surplusage and the amendment of the numbers of the subsequent SEQ IDs does not present new

matter. Reconsideration and withdrawal of this objection are therefore respectfully urged.

Claims 70, 77, 79 and 80 have been objected to as being in improper dependent form. The examiner states that claims 70 and 77 depend on claims 69 and 76, respectively, which in turn depend on claims 67 and 74, respectively. The examiner states that claims 70 and 77 say that nucleotides 459-602 encode amino acid residues 118-165 of SEQ ID NO:5, but the sequence alignment indicates that this is not the case.

As indicated above, the sequence listing has now been corrected to show that the amino acid at position 65 is Glu, rather than Gln. Accordingly, it is believed that this objection has now been obviated.

Furthermore, see applicant's response of August 21, 2001, which shows that other errors have already been corrected.

The examiner states that claims 79 and 80 are objected to because the parent claim 77 is drafted using the transitional phrase "consisting." This objection is respectfully traversed.

Claim 79 and 80 are not dependent from claim 77, but are dependent from claim 76, which does not use the "consisting of" language. Accordingly, this objection is based on an inaccurate assumption and should be withdrawn.

Claims 67-82 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written

description requirement. In the first part of this rejection, the examiner states that the claims are interpreted as drawn to a genus of products and method of using the genus of products. The examiner states that the only feature present in the claims is a partial sequence of residues 118-165 of SEQ ID NO:5 without an identification of any particular function associated with the partial sequence. Accordingly, the examiner states that, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. This rejection is respectfully traversed.

First of all, it is not understood why the examiner has included claims 74-82 in this rejection as the peptide produced by each of these claims consists of C48. Accordingly, these claims should be free of this part of the rejection. As to claims 67-73, the specification includes disclosure of C48, as well as the entire OFF1 of which C48 is a part. It is thus expected that other fragments of OFF1, of which C48 is a part, will have the same activity as has been shown in the present specification for C48. Accordingly, reconsideration and withdrawal of this part of the rejection are respectfully urged.

The examiner states that claims 67-82 are also rejected for new matter because SEQ ID NO:5 is new matter. The examiner states that the specification as originally filed does not have

support for "SEQ ID NO:5", "residues 118-165 of SEQ ID NO:5", and "nucleotides 459-602 of SEQ ID NO:1." Further, the examiner states that the specification as originally filed does not have support for "arthritis" and "rheumatoid arthritis" in claims 81 and 82. This part of the rejection is respectfully traversed.

It is not understood why the examiner states that the C48 fragment (residues 118-165 of SEQ ID NO:5 as recited in the claims) is not disclosed on the referenced pages and figures of the application. Page 21, lines 19-21, clearly states that C48 is the unique C-terminal 48 amino acids of the OFF1, i.e., residues 118-165. As discussed above, the presently-appearing SEQ ID NO:5 is the same as SEQ ID NO:6 in the PCT publication and is the sequence shown in Fig. 5 of the present specification. Accordingly, this sequence is definitely supported by this figure. The same figure establishes that nucleotides 459-602 of SEQ ID NO:1 encode amino acids 118-165 of SEQ ID NO:5

With respect to "arthritis" and "rheumatoid arthritis", the examiner's attention is invited to page 11, line 16, of the present specification, as well as Example 13, beginning on page 36 of the present specification (note line 17, for example) and Example 14 on page 39 of the present specification. Accordingly, the present specification has support for the terms noted by the examiner. Reconsideration and withdrawal of this new matter rejection are respectfully urged.

Claims 69-82 have been rejected under 35 U.S.C. §112, as failing to comply with the enablement requirement. The examiner states that the specification as originally filed does not teach how to make a protein comprising amino acid residues 118-165 of SEQ ID NO:5. This rejection is respectfully traversed.

Example 9 shows that C48 (i.e., amino acids 118-165 of SEQ ID NO:5) can be obtained from OFF1 by cleavage with restriction enzymes 5' EcoR1 and 3' Xho1. Furthermore, the full sequence is provided, and this can be obtained by an automatic sequencer. Accordingly, reconsideration and withdrawal of this part of the rejection are respectfully urged.

The examiner further states that there is no enablement in the specification because rheumatoid arthritis is notoriously difficult to treat. This part of the rejection is also respectfully traversed.

Example 13, beginning on page 36 of the present specification, shows an animal model for the treatment of arthritis. It is not necessary for an applicant to have clinical trials in order to show utility in the treatment of diseases as long as there are appropriate animal models in the specification. The examiner has not explained why the experiment in the specification would not be expected to create a reasonable expectation of success in the treatment of arthritis in humans.

Furthermore, claim 81 only reads on "treating" arthritis. "Treating" does not require a total cure, only amelioration. This would not be considered to be an incredible statement of utility, particularly in light of Example 13 in the present specification.

Furthermore, attached hereto is "C48/PLIF CIA Study Final Report," which has been issued recently by Serono International SA at the end of an evaluation period during which the effectiveness of the C48 and the treatment of rheumatoid arthritis was tested. The model used by Serono was the mouse model of Type 2 collagen-induced arthritis, which is known to be the best model for RA from which extrapolation into arthritis in humans may be made. The data presented in the Serono report is clearly highly positive with respect to prophylactic and therapeutic treatment of RA at the high C48 dosage, namely at 3 mg/kg. This information merely supplements the statements in the specification and the evidence submitted therein as to proof of effectiveness against arthritis in animal models. Reconsideration and withdrawal of this part of the rejection are also respectfully urged.

The examiner states that claims 72 and 79 are drawn to a host cell comprising the vector of previous claims but that the claims are broadly interpreted to encompass host cells that are not isolated and are comprised within an organism.

Claims 72 and 79 have now been amended to specify that they are directed to isolated host cells. Accordingly, these claims do not read on gene therapy or transgenic animals. Reconsideration and withdrawal of this part of the rejection are also respectfully urged.

It is submitted that all of the claims now present in the case clearly define over the references of record and fully comply with 35 U.S.C. §112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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TTGACACCAGACCAACTGGTAATGGTAGCGACCGGCGCTCAGCTGGAATTCCAAAAAATGT

AATGCACACTCCATTGCATTCAGCCCGCCTCTCCTTAGTCGCCGCC

met	thr	thr	ala	ser	thr	ser	gln	val	arg	gln
ATG	ACG	ACC	GCG	TCC	ACC	TCG	CAG	GTG	CGC	CAG
asn	tyr	his	gln	asp	ser	glu	ala	ala	ile	asn
AAC	TAC	CAC	CAG	GAC	TCA	GAG	GCC	GCC	ATC	AAC
arg	gln	ile	asn	leu	glu	leu	tyr	ala	ser	tyr
CGC	CAG	ATC	AAC	CTG	GAG	CTC	TAC	GCC	TCC	TAC
val	tyr	leu	ser	met	ser	tyr	tyr	phe	asp	arg
GTT	TAC	CTG	TCC	ATG	TCT	TAC	TAC	TTT	GAC	CGC
asp	asp	val	ala	leu	lys	asn	phe	ala	lys	tyr
GAT	GAT	GTG	GCT	TTG	AAG	AAC	TTT	GCC	AAA	TAC
phe	leu	his	gln	ser	his	glu	glu	arg	gln	his
TTT	CTT	CAC	CAA	TCT	CAT	GAG	GAG	AGG	GAA	CAT
ala	glu	lys	leu	met	lys	leu	gln	asn	gln	arg
GCT	GAG	AAA	CTG	ATG	AAG	CTG	CAG	AAC	CAA	CGA
gly	gly	arg	ile	phe	leu	gln	asp	ile	lys	lys
GGT	GGC	CGA	ATC	TTC	CTT	CAG	GAT	ATC	AAG	AAA
pro	asp	cys	asp	asp	trp	glu	ser	gly	leu	asn
CCA	GAC	TGT	GAT	GAC	TGG	GAG	AGC	GGG	CTG	AAT
ala	met	glu	cys	ala	leu	his	leu	glu	lys	asn
GCA	ATG	GAG	TGT	GCA	TTA	CAT	TTG	GAA	AAA	AAT
val	asn	gln	ser	leu	leu	glu	phe	pro	ser	pro
GTG	AAT	CAG	TCA	CTA	CTG	GAA	TTC	CCT	TCT	CCT
ile	ser	pro	ser	pro	ser	cys	trp	his	his	thr
ATC	TCT	CCC	AGT	CCT	AGC	TGC	TGG	CAT	CAC	TAT
thr	thr	asn	arg	pro	glu	pro	gln	his	his	leu
ACT	ACT	AAC	AGA	CCG	CAA	CCT	CAA	CAC	CAC	CTT
leu	arg	pro	arg	arg	arg	lys	arg	pro	his	ser
CTT	CGA	CCC	CGC	CGG	AGG	AAG	AGA	CCC	CAT	TCT
ile	pro	thr	pro	ile	leu	ile	phe	arg	ser	pro
ATA	CCA	ACA	CCT	ATT	CTG	ATT	TTT	CGG	TCA	CCC

TGA AGTTTATATTCTTATCCTACCAGGCTTCGGAATAATCTCCCATATTGTAACTTAC

TACTCCGGAAATCGCTGTCGCCTAACCGCTAACATTACTGCAGGCCACCTACTCATGCAC

CTAATTGGAAGCGCCACCCTAGCAATATCAACCATTAACCTTCCCTCTACACTTATCATC

TTCACAATTCTAATTCTACTGACTATCCTAGAAATCGCTGTCGCCTTAATCCAAGCCTAC

GTTTTCACACTT~~XXXXXXXXXXXXXXXXXXXX~~ CTAGTAA GCCTCTACCTGCACGACAA CACAT AAAAAAAA

Fig. 5